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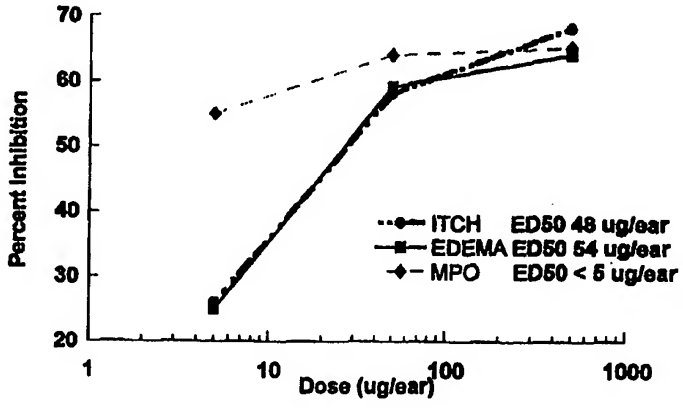
(54) Title: NOVEL USE OF COMPOUNDS FOR ANTI-PRURITIC ACTIVITY

Anti-Pruritic Activity of Compound I



(57) Abstract

Derivatives of 8–substituted xanthines which are used in the prophylactic or therapy of diseases or disorders which have a pruritic component.

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NOVEL USE OF COMPOUNDS FOR ANTI-PRURITIC ACTIVITY

FIELD OF INVENTION

The present invention relates to compounds which are of use in the treatment and management of pruritis.

BACKGROUND OF THE INVENTION

Pruritis is a common symptom of many inflammatory skin diseases, notably psoriasis and atopic dermatitis. This symptom has historically been difficult to model. Recently, a behavioral model for peripherally evoked itch was published (Woodward et al., Characterization of a behavioral model for peripherally evoked itch suggests platelet-activating factor as a potent pruritogen. J. Pharmacol. Exp. Therap. 272:758-765, 1995). This model has lead to additional modifications as will be shown herein.

As little effective treatment for this condition exists, there remains a need for treatment, in this field, for compounds which are capable of anti-pruritic activity.

SUMMARY OF THE INVENTION

This invention relates to the novel use of PDE_4 inhibitors, preferably compounds of Formula (I) for the prophylaxis, treatment and management of pruritis in a mammal, including humans, in need of such treatment, which method comprises administering to such mammal, an effective amount of a compound of Formula (I).

The compounds of the present invention of Formula (I) are described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure I demonstrates the anti-pruritic activity of compound I, 1,3-di-cyclopropylmethyl-8-amino xanthine in an arachidonic acid induced pruritis model.

DETAILED DESCRIPTION OF THE INVENTION

The present invention has found that PDE4 inhibitors, as a class of compounds, regardless of structure possess anti-pruritis activity. As pruritis is a key symptom of many different disease states, the use of PDE4 inhibitors in the managment of pruritic activity is of great value.

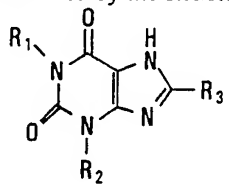
While it is recognized that PDE_4 compounds are of many different structural classes, they all share a common feature, inhibition of the PDE_4 isoenzymes. A

skilled artisan, using well known and defined assays, will be able to determine if a compound is an inhibitor of the PDE_4 isoenzymes, and be of use herein. Suitable PDE_4 compounds for use herein include, but are not limited to, those described in WO 92/00968; PCT/US91/08229; WO 92/05175; WO 92/05176; WO 92/11260; WO 93/01014; PCT/US92/03613; WO 93/07111; PCT/US93/02045; WO 93/19748; WO 93/19750; WO 93/19751; WO 93/19747; WO 93/19749; WO 93/19720; WO 94/20079; WO 95/00139; WO 95/08581; WO 95/09308; WO 95/09623; WO 95/09836; WO 95/09624; WO 95/09837; WO 95/09627; WO 95/24381; WO 95/27692; WO 96/19995; WO 96/20158; WO 96/20153; WO 96/19980; WO 96/19988; WO96/19977; WO 96/20161; WO 96/20157; PCT/US95/16707; WO 96/20690; WO 96/20159; WO 96/19983; WO 96/19984; WO 96/19985; WO 96/19990; WO 96/19994; WO 96/20163; WO 96/20156; WO 96/19986; WO 96/20174; WO 96/19979; WO 96/20160 WO 96/20175; WO 96/19993; WO 96/20162; WO 96/19978; WO 96/23754; WO 96/36594; ; WO 97/03945, US 5,734,051 and US 5,420,154. Suitable assays for determination of PDE_4 activity are also described in the above noted references, whose disclosures are incorporated by reference herein in their entirety.

A particular PDE_4, CP 80633 is described in J.M. Hanifin et al. J. Invest. Dermatol. 107:51-56 (1996). Preferably, the method of use does not include the compound CP80633.

The compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of such treatment for pruritis. Treatment, may be therapeutically or prophylactically in animals .

The compounds of the present invention of Formula (I), are described in US Patent 5,734,051 and are represented by the structure:



(I)

wherein

R_1 and R_2 are each independently alkyl or a moiety of the formula

$$-(CH_2)_m-A;$$

m is a number from 0 to 3;

A is an unsubstituted or substituted cyclic hydrocarbon radical;

R_3 is halogen, nitro, or $-NR_4R_5$;

R_4 and R_5 are independently hydrogen, alkyl, alkylcarbonyl or together with the nitrogen to which they are attached forming an optionally substituted heterocyclic ring; and the pharmaceutically acceptable salts thereof.

Preferably both R_1 and R_2 represent $-(CH_2)_m-A$. Preferably the A moiety represents a C_{3-8} cycloalkyl group, particularly a C_{3-6} cycloalkyl and preferably unsubstituted. More preferably A is a cyclopropyl or cyclobutyl moiety. Preferably m is zero or one. Suitable optional substituent groups for any cyclic hydrocarbon include a C_{1-6}alkyl moiety or halogen atom.

A preferred group for R_1 or R_2 is an alkyl group of 1 to 6 carbons, specifically methyl, ethyl, propyl or n-butyl. More preferred is n-butyl.

When R_3 is halogen, the preferred substitution is bromine or chlorine.

When R_3 is $-NR_4R_5$, and R_4 and R_5 represent alkyl or alkylcarbonyl, it is preferred that one of R_4 or R_5 is hydrogen.

Suitable heterocyclic groups include saturated or unsaturated heterocylic groups having single or fused rings, each ring having 5 to 7 ring atoms which ring atoms optionally comprise up to two additional hetero atoms selected from O, N, or S.

Preferred heterocyclic groups include single rings comprising 5 to 7 ring atoms, more preferably 5 to 6 ring atoms,and most preferably 6 ring atoms. Preferred heterocyclic groups are pyrrolidinyl, piperidinyl, or morpholinyl rings.

Specifically exemplified compounds of Formula (I) are:

1,3-di-n-butyl-8-nitro xanthine;
1,3-di-cyclopropylmethyl-8-nitro xanthine;
1,3-di-cyclobutylmethyl-8-nitro xanthine;
1,3-di-cyclopentylmethyl-8-nitro xanthine;
1,3-di-cyclohexylmethyl-8-nitro xanthine;
1,3-di-n-butyl-8-amino xanthine;
1,3-di-cyclopropylmethyl-8-amino xanthine;
1,3-di-cyclobutylmethyl-8-amino xanthine;
1,3-di-cyclopentylmethyl-8-amino xanthine;
1,3-di-cyclohexylmethyl-8-amino xanthine;
1,3-di-cyclopropyl-8-amino xanthine;
1,3-di-n-butyl-8-acetamido xanthine;

1,3-di-n-butyl-8-chloro xanthine;
1,3-di-n-butyl-8-bromo xanthine;
1,3-di-cyclopropylmethyl-8-chloro xanthine;
1,3-di-cyclohexyl-8-chloro xanthine;
1,3-di-n-butyl-8-piperidino xanthine;
1,3-di-cyclopropylmethyl-8-morpholino xanthine;
1,3-di-n-butyl-8-pyrrolidinyl xanthine;
1,3-di-cyclopropylmethyl-8-pyrrolidinyl xanthine;
1,3-di-cyclopropylmethyl-8-piperidinyl xanthine;
1,3-di-cyclohexylmethyl-8-piperidinyl xanthine;
1,3-di-cyclohexylmethyl-8-bromo xanthine; and
1,3-di-cyclohexyl-8-nitro xanthine; or the pharmaceutically acceptable salts thereof.

The most preferred compound of Formula (I) for use in the method of this invention is 1,3-di-cyclopropylmethyl-8-amino xanthine or a pharmaceutically acceptable salt thereof.

By the term "alkyl" groups as used herein, alone or when used as part of another group (for example as in alkylcarbonyl) is meant to include both straight or branched chain radicals of 1 to 12 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

By the term "cyclic hydrocarbon", unless specified otherwise, as used herein is meant a single ring or a fused rings of 3 to 8 carbon atoms. Cyclic hydrocarbons may comprise up to 8 carbons in each ring. The term "cycloalkyl" or "cycloalkyl alkyl" as used herein is meant to be interchangeable with the term "cyclic hydrocarbon". Cycloalkyl and cycloalkyl-alkyl groups are meant to include, but not limited to cyclopropyl, cyclopropyl-methyl, cyclopentyl or cyclohexyl.

By the term "halo" as used herein is meant all halogens, i.e., chloro, fluoro, bromo and iodo.

METHODS OF PREPARATION

The preparation of the compounds of Formula (I) can be carried out by one of skill in the art according to the procedures outlined herein, and as described in Maschler et al., Great Britain Patent Application No. 8906792.0 filed on March 23,

1989, and US Patent No. 5,734,051 whose entire disclosures are incorporated herein by reference in its entirety.

METHODS OF TREATMENT

The compounds of Formula (I) or a pharmaceutically acceptable salt thereof can also be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or or unregulated pruritic activity.

The compounds of Formula (I) may be used topically in the treatment or prophylaxis of topical disease states which have a pruritic component.

The compounds of Formula (I) are disclosed in Maschler et al., Great Britain Patent Application No. 8906792.0 filed on March 23, 1989, and US Patent 5,734,051 for the treatment of disorders associated with increased numbers of eosinophils, such as proliferative skin disease states, i.e. psoriasis, atopic dermatitis, non-specific dermititis, primary irritant contact dermatitis, allergic contact dermititis, or allergic disorders such as atopy, uticaria, eczema, rhinitis, serborrheic dermatitis, and mange in domestic animals. The compounds of Formula (I) are also disclosed in PCT/US91/08734, and PCT/US93/01496 published as WO 93/06699 whose dislosures are incorporated herein by reference in its entirety, for the treatment of tumour necrosis mediated diseases.

The compounds of Formula (I) may, be administered concurrently with another agents useful for the treatment or managment of pruritis, such as steroids.

It will be recognized by one of skill in the art that the actual amount of a monokine activity interfering agent required for therapeutic effect will, of course, vary with the agent chosen, the route of administration desired, the nature and severity of the disease, and the particular condition of the mammal, specifically human, undergoing treatment, and is ultimately at the discretion of the physician. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of the agent will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the agent given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The compounds of Formula (I) may be administered orally (when active by this route), topically, parenterally or by inhalation in conventional dosage forms

prepared by combining such agent with standard pharmaceutical carriers according to conventional procedures in an amount sufficient to produce therapeutic activity.

The pharmaceutical carrier employed can be readily determined by one of skill in the art who will recognize that such determination will depend upon various well-known factors such as the nature, quantity and character of the particular monokine activity interfering agent being employed and the form and route of administration desired. The carriers employed may be those described elsewhere herein.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The pharmaceutical composition of the present invention will comprise an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent. The compounds of Formula (I) are administered in conventional dosage forms prepared by combining a compound of Formula (I) in an amount sufficient to produce activity, respectively, with standard pharmaceutical carriers according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, polyethylene glycol, coconut oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

Compounds of Formula (I) and their pharmaceutically acceptable salts can be employed in a wide variety of pharmaceutical forms. The preparation of a pharmaceutically acceptable salt will be determined by the nature of the compound itself, and can be prepared by conventional techniques readily available to one skilled in the art. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1 gram. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a

hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, polyethylene glycol, coconut oil, glycerine or water with a flavouring or colouring agent.

The amount of a compound of Formula (I) required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the inflammatory condition and the animal undergoing treatment, and is ultimately at the discretion of the physician.

The term 'parenteral' as used herein includes intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, preferably about 0.01 mg/Kg to 20 mg/Kg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The compounds of Formula (I) may be administered orally. The daily dosage regimen for oral administration is suitably about .1 mg/kg to 1000mg day. For administration the dosage is suitably about .001mg/kg to 40mg/kg, preferably about 0.01 to 20 mg/Kg of a compound of formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit activity.

The compounds of Formula (I) may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage regimen for inhalation administration is suitably about .001 mg/kg to 40mg/kg, preferably 0.01 to 20 mg/Kg of a compound of formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

The compounds of Formula (I) may also be administered topically. By topical administration is meant non-systemic administration and includes the application of a compound of Formula (I) externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. The daily dosage regimen for topical administration is suitably about .001 mg/kg to 100mg/kg, preferably 0.1 to 20 mg/Kg of a compound of formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour.

Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or macrogols. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactants such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient, a compound of Formula (I), with which it is to be combined, the route of administration and other well-known variables.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable

salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

FORMULATION EXAMPLES

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of liquid formulations are given below.

1. A solution containing a compound of Formula (I) is prepared by dissolving the compound in water, or other suitable carrier, with or without a preservative, such as benzoic acid, to deliver the desired amount of drug per use. The compound is present in an amount from about 10μg to about 30 μg/ per ml of carrier.

2. A solution containing a compound of Formula (I) is prepared by dissolving the compound in an amount from about 1 to about 10mg per ml of PEG 400 with or without BHA/BHT preservatives. The solution can alternatively be filled into a soft gelatin capsule to prepare a solid oral dosage form or used as a syrup.

3. A solid dosage form containing a compound of Formula (I), such as 1,3-di-cyclopropylmethyl-8-amino xanthine has been prepared by mixing 50mg of the compound with various concentration (mg) of mannitol, hydroxypropylmethylcellulose, calipharm, Starch 1500, and magnesium sterate (as a lubricant), to fill capsules of an appropriate size or the composition may, if desired, be compressed into tablets. Various formulation of the ingredients are presented in Table 1, numbered from 1 to 6.

UTILITY EXAMPLES

The method described in the Woodward et al. manuscript, *supra*, served as the protoype for the mouse model which developed in the present invention. The mouse model takes advantage of the cutaneous inflammatory response to arachidonic acid which is preceeded by scratching and rubbing behavior indicative of pruritis..

Briefly. Balb/c mice were administered a topical dose of arachidonic acid (2 mg/ear) in 20 ul cold acetone to the left ear. The treated mice were then placed individually into 4L beakers. After a 2 min accommodation period, the episodes of scratching and head shaking were counted over a 10 min period. The data were analysed by calculating the mean and standard error. A statistical difference in the mean values was determined using Student's t-test. The biochemical pharmacology of the inflammatory response to arachidonic acid has implicated mast cell degranulation and eicosanoid inflammatory mediator release (e.g. leukotrienes and prostanoids). Tachykinins and platelet activating factor may also be involved in this response. The

anti-inflammatory activity of phosphodiesterase type 4 (PDE4) inhibitors was also demonstrated using arachidonic acid (Griswold, D.E.et al., Pharmacology of the pyrroloimidazole, SK&F 105809. Antiinflammatory activity and inhibition of mediator production in vivo. Biochemical Pharmacology 42:825-831,1991) whose disclosure is incorporated by reference herein in its entirety.

Specific Methods:

Male Balb/c mice (n=6/treatment group) weighing 19-23 grams were administered a topical dose of arachidonic acid (2 mg/ear) in 20 ul cold acetone to the left ear. Immediately after that application, vehicle or test compound was applied to the same ear in a volume of 25 ul. Doses varied from 5 to 1000 ug/ear. The treated mice were then placed individually into 4L beakers. After a 2 min accommodation period, the episodes of scratching and head shaking were counted over a 10 min period. The data were analysed by calculating the mean and standard error. A statistical difference in the mean values was determined using Student's t-test.

It was of interest, therefore to determine if PDE_4 inhibitors of different structural classes would demonstrate anti-pruritic activity in this model. As indicated below, three such PDE_4 inhibitors did demonstrate signficant anti-pruritic activity.

Topical Anti-pruritic Acitivity of PDE4 Inhibitors

Treatment (100 ug/ear)	Inhibition of Pruritis (%)
BRL 61063	61.4***
Rolipram	75.8***
CP 80633	49.7***

***, Statistically significant at a $p < 0.001$ versus vehicle control, BRL 61063 is the same as Compound I.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

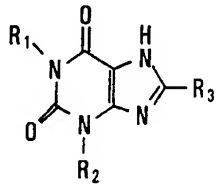
The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments

specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the are can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed is

1. A method of treating pruritis in a mammal in need thereof which comprises administering to such mammal an effective amount of a compound of a PDE_4 inhibitor, other than CP 80633.

2. The method according to Claim 1 wherein the PDE_4 inhibitor is a compound of the formula:



(I)

wherein

R_1 and R_2 each independently represent alkyl or $-(CH_2)_m-A$;

m represents zero or an integer 1, 2 or 3;

A represents a substituted or unsubstituted cyclic hydrocarbon radical;

R_3 represents a halogen atom, a nitro group, or a group $-NR_4R_5$;

R_4 and R_5 each independently represent hydrogen, alkyl or alkylcarbonyl; or R_4 and R_5 together with the nitrogen to which they are attached form an optionally substituted heterocyclic group; and the pharmaceutically acceptable salts thereof.

3. The method according to claim 2, wherein R_1 represents $-(CH_2)_m-A$.

4. The method according to claim 2, wherein R_1 and R_2 both independently represent $-(CH_2)_m-A$.

5. The method according to claim 4 wherein A represents a substituted or unsubstituted C_{3-8} cycloalkyl group.

6. The method according to claim 4, wherein m represents 1.

7. The method according to claim 6, wherein A represents a substituted or unsubstituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

8. The method according to claim 7, wherein A represents a cyclopropyl group or a cyclobutyl group.

9. The method according to claim 8, wherein R_3 is nitro, or $-NR_4R_5$ wherein R_4 is hydrogen and R_5 is hydrogen or alkylcarbonyl.

10. The method according to claim 9, wherein R_4 or R_5 is hydrogen.

11. The method according to claim 10, wherein A represents a cyclopropyl group.

12. The method according to claim 2 wherein the compound is selected from the group consisting of:
1,3-di-n-butyl-8-nitro xanthine;
1,3-di-cyclopropylmethyl-8-nitro xanthine;
1,3-di-cyclobutylmethyl-8-nitro xanthine;
1,3-di-cyclopentylmethyl-8-nitro xanthine;
1,3-di-cyclohexylmethyl-8-nitro xanthine;
1,3-di-n-butyl-8-amino xanthine;
1,3-di-cyclopropylmethyl-8-amino xanthine;
1,3-di-cyclobutylmethyl-8-amino xanthine;
1,3-di-cyclopentylmethyl-8-amino xanthine;
1,3-di-cyclohexylmethyl-8-amino xanthine;
1,3-di-cyclopropyl-8-amino xanthine;
1,3-di-n-butyl-8-acetamido xanthine;
1,3-di-n-butyl-8-chloro xanthine;
1,3-di-n-butyl-8-bromo xanthine;
1,3-di-cyclopropylmethyl-8-chloro xanthine;
1,3-di-cyclohexyl-8-chloro xanthine;
1,3-di-n-butyl-8-piperidino xanthine;
1,3-di-cyclopropylmethyl-8-morpholino xanthine;
1,3-di-n-butyl-8-pyrrolidinyl xanthine;
1,3-di-cyclopropylmethyl-8-pyrrolidinyl xanthine;
1,3-di-cyclopropylmethyl-8-piperidinyl xanthine;
1,3-di-cyclohexylmethyl-8-piperidinyl xanthine;
1,3-di-cyclohexylmethyl-8-bromo xanthine; and
1,3-di-cyclohexyl-8-nitro xanthine; or if appropriate, a pharmaceutically acceptable salt thereof.

13. The method according to Claim 2 wherein the compound is 1,3-di-cyclopropylmethyl-8-amino xanthine or a pharmaceutically acceptable salt thereof.

14. The method of Claim 2 or 13 wherein the compound is administered orally, parenterally, topically or by inhalation.

15. The method according to Claim 14 wherein the compound is administered topically.

16. The method according to Claim 1 wherein the compound is administered topically with an effective amount of a second anti-pruritic compound.

17. The method according to Claim 1 wherein the compound is described in WO 92/00968; PCT/US91/08229; WO 92/05175; WO 92/05176; WO 92/11260; WO 93/01014; PCT/US92/03613; WO 93/07111; PCT/US93/02045; WO 93/19748; WO 93/19750; WO 93/19751; WO 93/19747; WO 93/19749; WO 93/19720; WO 94/20079; WO 95/00139; WO 95/08581; WO 95/09308; WO 95/09623; WO 95/09836; WO 95/09624; WO 95/09837; WO 95/09627; WO 95/24381; WO 95/27692; WO 96/19995; WO 96/20158; WO 96/20153; WO 96/19980; WO 96/19988; WO96/19977; WO 96/20161; WO 96/20157; PCT/US95/16707; WO 96/20690; WO 96/20159; WO 96/19983; WO 96/19984; WO 96/19985; WO 96/19990; WO 96/19994; WO 96/20163; WO 96/20156; WO 96/19986; WO 96/20174; WO 96/19979; WO 96/20160 WO 96/20175; WO 96/19993; WO 96/20162; WO 96/19978; WO 96/23754; WO 96/36594; ; WO 97/03945, US 5,734,051 and US 5,420,154.

18. A method of treating pruritis in a mammal in need thereof which comprises administering to such mammal an effective amount of the compound 1,3-di-cyclopropylmethyl-8-amino xanthine, or a pharmaceutically acceptable salt thereof.

19. The method of Claim 18 wherein the compound is administered orally, parenterally, topically or by inhalation.

20. The method according to Claim 19 wherein the compound is administered topically.

21. The method according to Claim 18 wherein the compound is administered topically with an effective amount of a second anti-pruritic compound.

22. The method according to Claim 21 wherein the second anti-prutitic compound is a steroid.

Anti-Pruritic Activity of Compound I

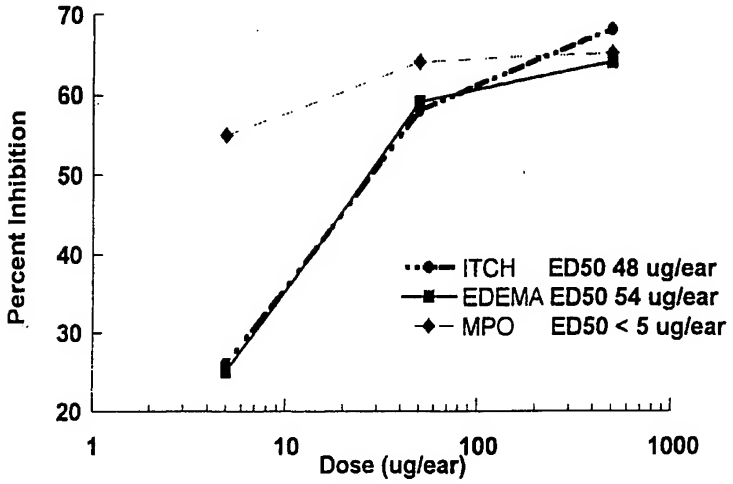


FIGURE 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/21886

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/52, 31/535
US CL :514/234.2, 262

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/234.2, 262

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS on-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,409,934 A (SMITH ET AL.) 25 April 1995, see entire document, especially column 11, lines 58-65.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
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Date of the actual completion of the international search	Date of mailing of the international search report
14 JANUARY 1999	02 FEB 1999

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